Infectious Diseases Society of America

Re: Review of Lyme Disease Guidelines

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Issues relating to the 2006 Lyme Disease Guidelines:

I am the mother of a teenaged boy who suffered from undiagnosed Lyme disease, but has subsequently made a complete recovery. As a trained entomologist, I was fortunate in being able to find ways to get my son diagnosed and treated in spite of widespread misunderstandings of the limitations of the current IDSA guidelines within the North American medical community. As a result of my experiences, I am now an active volunteer assisting Lyme sufferers, as well as a board member of the Canadian Lyme Disease Foundation.

I firmly believe that the IDSA guidelines, as they stand, require revision. The current version of the IDSA guidelines is incomplete, and this inadequacy extends across the clinical assessment, treatment and prevention of Lyme disease. Limitations in serological testing are underplayed in the IDSA guidelines, and reference to the cystic form of Lyme is unhelpfully skeptical of the clinical significance of this important form of the disease-causing organism.

The base assumption, in the IDSA guidelines, that current serological testing detects all North American strains of *Borrelia burgdorferi* is unsupported. Diversity of *B. burgdorferi* and its related species in North America is mentioned only in passing and the guidelines stress that only *B. burgdorferi* is pathogenic in North America (page 1096 Wormser *et al* 2006, and continues to be assumed e.g. Craig-Mylius *et al* 2009). This stance downplays *Borrelia lonestari* (page 1098), even though credible researchers such as Burkot *et al* (2001) and Stromdahl *et al* (2003) caution that human disease may result from this variant of the *burgdorferi*

species complex. There is no mention of the fact that *Borrelia garinii*, the most neurotropic of the European strains, has been documented in North America in both the US and Canada (Smith *et al* 2006). Since the guidelines were written, *Borrelia bissettii* and *B. carolinesis* have been described as new species in the complex (Schneider *et al* 2008, Rudenko *et al* 2009) and *B. bissettii* has been shown to be pathogenic (Schneider *et al* 2008). Even within strain B31 of *B. burgdorferi* itself, nine distinct clonal lineages have been described from a single field site in the northeast US (Bunikis *et al* 2004). Fitness differences have subsequently been demonstrated for some of these different clonal lineages by Hanincova *et al* (2008). Additional research has shown that at least 12 distinct strains coexist in the northeastern USA, based on DNA sequence differences in outer surface protein C (Qiu *et al* 2008). Nowhere do the IDSA guidelines mention that this extensive diversity is not necessarily detected by current serological tests.

In addition to ignoring genetic diversity in *B. burgdorferi* and related species, chronic infection is considered to be highly implausible. However, *Borrelia* are clearly capable of persistent infection and such persistence is the norm in mice, rats, hamsters, dogs and monkeys (Barthold 2000, Straubinger 2000, Summers *et al*. 2005, Hodzic *et al*. 2008). Persistence of *Borrelia* has also been well documented to occur in humans (Breier *et al*. 2001, Holl-Weiden *et al* 2007, Hunfeld *et al*. 2005, Oksi *et al*. 1999), as well as immune evasion (Bankhead and Chaconas 2007, Liang *et al*. 2002, Xu *et al*. 2008). Intracellular localization is known within endothelial cells (Ma *et al*. 1991, Thomas *et al*. 1994), synovial cells (Girschick *et al*. 1996) and neuronal and glial cells (Livengood and Gilmore 2006). Infiltration of blood vessels, cardiac myocytes and collagen tissues has been shown (Pachner *et al*. 1995), and adherence and escape of *Borrelia* from vasculature has recently been visualized directly by Moriarty *et al*. (2008). Sequestration and physical protection from the immune system in the extracellular matrix have been reviewed by Cabello *et al*. (2007). Yet on page 1117 of the IDSA guidelines, there is a statement that 'The notion that symptomatic, chronic *B. burgdorferi* infection can exist … is highly implausible …'. Such dismissal of a body of rigorous, peer-reviewed literature is unfathomable.

Treatment of Lyme disease has been heavily influenced by Klempner *et al* 2001 (i.e. page 1116 of IDSA guidelines) without mention of the obvious flaws in that study. Until they can be definitively refuted, criticisms of these trials, such as those of Cameron (2006 and later 2009a) should be taken seriously in any IDSA

guideline revisions. Currently the IDSA guidelines dismiss post-Lyme disease syndromes as an omnibus category, and state that 'posttreatment symptoms appear to be more related to the aches and pains of daily living' (page 1115), which is again rebutted by Cameron (2009b). Livengood and Gilmore (2006) have demonstrated that *B. burgdorferi* is able to invade human neuronal and glial cells, where the spirochete cells are protected from gentamycin. Cabello *et al* (2007) and Embers *et al* (2004) have reviewed literature that consistently demonstrates that sequestration in immune privileged sites, antigenic variation and suppression of host immune responses are extremely important in understanding the basis of infection by *B. burgdorferi*. As well, Yrjanainen *et al* (2007) note that spirochetes can successfully avoid the lethal effects of ceftriaxone without losing their infectivity. Fallon *et al* (2008) have demonstrated that long term IV therapy can be unable to sustain cognitive gains in Lyme patients, and this further suggests that treatment for the cystic form of *B. burgdorferi* should be investigated. However, the current IDSA guidelines appear to ignore this evidence, stating instead that metronidazole and tinidazole are not recommended because of 'lack of biological plausibility' (page 1105) and 'The "cystic" forms …. have not been shown to have any clinical significance' (page 1118). This is in spite of prior publication of the widely known work of Brorson and Brorson (1999 and 2004). The Brorson and Brorson (2004) study has since been supported by Margulis *et al* (2009), a position paper that makes reference to an extensive body of Russian research. More recent work by Miklossy *et al* (2008) in North America has independently confirmed the existence of the cystic form and its role in human disease. Both Miklossy *et al* (2008) and Margulis *et al* (2009) caution that a full understanding of the serology of Lyme disease must include the atypical forms as well as typical spirochetal forms. Continued lack of consideration of these findings in IDSA guidelines constitutes a serious and potentially damaging gap in the understanding of medical practitioners who rely on them.

A further shortcoming of the IDSA guidelines is that while limitations of PCR testing for *Borrelia* are stressed, the limitations of widely used ELISA and Western blots are not. On page 1110 of the IDSA guidelines, there is a statement that 'positive PCR results for a joint fluid specimen from a seronegative patient, however, should be regarded with skepticism.' This statement is dangerously misleading. For example, Holl-Weiden *et al* (2007) have demonstrated that a positive PCR in a seronegative child allowed treatment and reduced suffering and in fact it is biologically implausible that a positive PCR backed by clinical

symptoms would be a false positive, especially when a positive response to antibiotics is seen.

At the very least, limitations of ELISA and Western blots should be discussed in the IDSA guidelines. There is considerable debate over the sensitivity of ELISA assays, especially in late stages of the disease (e.g. Donta 2007, Stricker and Johnston 2008, Wilson 2007). The meta-analysis by Aguero-Rosenfeld *et al*. (2005) reports that ELISA sensitivity is less than 50% in the acute phase of an EM rash and only about 80% in the convalescent phase after antimicrobial treatment for an EM rash or a Lyme diagnosis has been obtained due to neurological involvement. Only the arthritic form of Lyme disease was associated with a higher sensitivity for ELISA in Aguero-Rosenfeld *et al*. (2005), even though this form constitutes only one of many strains even within the *B. burgdorferi* species complex (Tilley *et al* 2008). In Europe, false negative serology is considered a significant risk in neuroborreliosis unless multiple strains of *Borrelia* are tested for (Kaiser 2000, Jovicic *et al*. 2003).

In order to confirm a Lyme diagnosis according to the IDSA guidelines, it is considered necessary to document seroconversion from IgM to IgG about 4 weeks or more after infection (Aguero-Rosenfeld *et al*. 2005, Wormser *et al* 2006). However, the immunological response to Lyme disease is not that simple in some people, since seronegativity with only a cell-mediated immune response is clearly possible (Singh and Girschick 2004). In addition, detection of antibodies that are tied up in complexes would be missed by standard tests that rely on free antibodies (Holl-Weiden *et al*. 2007, Singh and Girschick 2004).

In short, the statements in the IDSA guidelines that there is 'no convincing biologic evidence' and 'lack of biologic plausibility' (page 1094) as well as 'There is no convincing evidence in North America for the persistence of *B. burgdorferi'* (page 1117) do not take into account the fact that the biology of *B. burgdorferi* is complex and incompletely understood. The current guidelines make no mention of the unique characteristics of *B. burgdorferi,* which include enormous potential for genomic adaptation. This spirochete has over twenty plasmids, both linear and circular, in addition to its one large linear chromosome, and this structure gives *B. burgdorferi* the greatest number of plasmids described for any living organism (Chaconas 2005, Tourand *et al* 2009). In addition, *B. burgdorferi* is unusual in using manganese for electron transport instead of iron (Posey and Gherardini 2000,

Ouyang *et al*. 2009), allowing the spirochetes to evade lactoferrin defense. Furthermore, antigenic variation at vlsE by recombination of cassette fragments demonstrably allows a large number of antigenically distinct variants to be produced and therefore aids in avoidance of the host immune system (Bankhead and Chaconas 2007).

In Europe, it is widely recognized that improved patient outcome is the true goal that everyone is seeking. This insight has allowed researchers like Clarissou *et al* (2009) to step back from the tension involved in the use of the term Lyme disease and to substitute 'Tick Associated Poly Organic Syndrome', or TAPOS, as a more neutral designation.

The bottom line is that it is too early to codify treatment for Lyme disease. I trust that you will consider the full breadth of the available research in your desperately needed review of the diagnosis and treatment of Lyme disease. The key will be to include a strongly worded statement that serological testing for Lyme disease suffers from extreme limitations. This will more effectively alert medical practitioners to the true state of the fast-evolving field of Lyme disease research, rather than leaving them with the impression, from the current IDSA guidelines, that the diagnosis and treatment of Lyme disease have been sufficiently defined to ensure the health of Americans and Canadians.

Sincerely,

Janet L.H. Sperling

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